Appendix 2

Clean copy of amended claims 21, 23, 27, 29, 31, 33-40, 98, and 100-106 (37 C.F.R. §1.121(c)(i)).

D1 6 ~~21~~. (Once amended) The method of claim ~~102~~ 1, which is for improving naturally-occurring vision in an animal, in the absence of any ophthalmologic disorder, disease, or injury.

D2 7 ~~23~~. (Once amended) The method of claim ~~102~~ 1, wherein the compound is administered to said animal in combination with an effective amount of one or more factor(s) useful in treating vision disorders, improving vision, treating memory impairment, or enhancing memory performance in an animal.

D3 9 ~~27~~. (Once amended) The method of claim ~~102~~ 1, wherein the nerve-related vision disorder is retinal ischemia.

D4 11 ~~29~~. (Once amended) The method of claim ~~102~~ 1, wherein the nerve-related vision disorder is optic nerve transection.

D5 13 ~~31~~. (Once amended) The method of claim ~~102~~ 1, wherein the nerve-related vision disorder is diabetes.

131 D

15 33. (Once amended) The method of claim 1 02, wherein the nerve-related vision disorder is macular degeneration.

16 34. (Once amended) The method of claim 1 02, wherein the nerve-related vision disorder is glaucoma related degeneration.

17 35. (Once amended) The method of claim 1 02, wherein the nerve-related vision disorder is cataract related degeneration.

18 36. (Once amended) The method of claim 1 02, wherein the nerve-related vision disorder is a detached retina.

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19 37. (Once amended) The method of claim 1 02, wherein the nerve-related vision disorder is inflammation related degeneration.

20 38. (Once amended) The method of claim 1 02, wherein the nerve-related vision disorder is photoreceptor degeneration.

21 39. (Once amended) The method of claim 1 02, wherein the nerve-related vision disorder is optic neuritis.

22 40. (Once amended) The method of claim 1 02, wherein the nerve-related vision disorder is dry eye degeneration.

207 23 98. (Once amended) The method of claim 102, wherein the compound has an affinity for an FKBP-type immunophilin.

25 100. (Once amended) The method of claim 102, wherein the compound is immunosuppressive.

26 101. (Once amended) The method of claim 102, wherein the compound is non-immunosuppressive.

1 102. (Once amended) A method for treating a nerve-related vision disorder, improving vision, treating memory impairment, or enhancing memory performance in an animal, which comprises administering to said animal an effective amount of a compound selected from the group consisting of:

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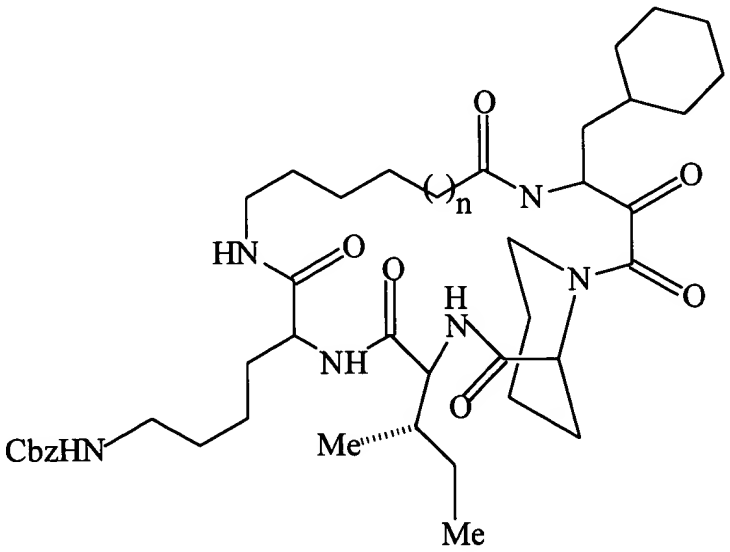
T1330



wherein n is 1; 2; or 3;

133

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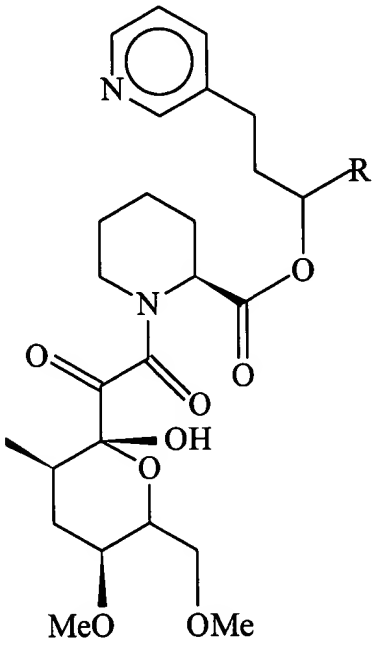
4-(4-methoxyphenyl)butyl (2S)-1-[2-(3,4,5-trimethoxyphenyl)acetyl]hexahydro-2-pyridinecarboxylate;

4-(4-methoxyphenyl)butyl (2S)-1-[2-(3,4,5-trimethoxyphenyl)acryloyl]hexahydro-2-pyridinecarboxylate;

4-(4-methoxyphenyl)butyl (2S)-1-[2-(3,4,5-trimethoxyphenyl)propanoyl]hexahydro-2-pyridinecarboxylate;

4-(4-methoxyphenyl)butyl (2S)-1-[2-oxo-2-(3,4,5-trimethoxyphenyl)acetyl]hexahydro-2-pyridinecarboxylate;



;

3-cyclohexylpropyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)hexahydro-2-pyridinecarboxylate;

3-phenylpropyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)hexahydro-2-pyridinecarboxylate;

3-(3,4,5-trimethoxyphenyl)propyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)hexahydro-2-pyridinecarboxylate;

(1R)-2,2-dimethyl-1-phenethyl-3-butenyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)hexahydro-2-pyridinecarboxylate;

(1R)-1,3-diphenylpropyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)hexahydro-2-pyridinecarboxylate;

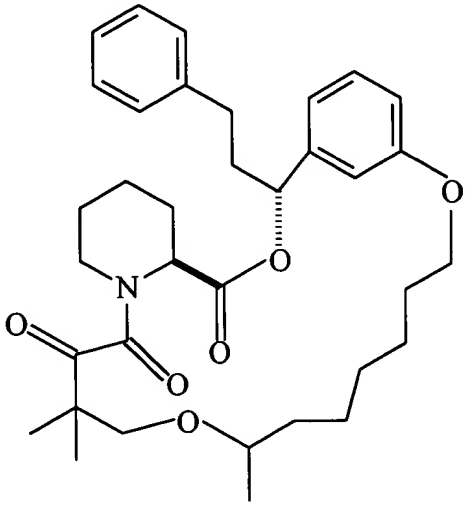
(1R)-1-cyclohexyl-3-phenylpropyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)hexahydro-2-pyridinecarboxylate;

(1S)-1,3-diphenylpropyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)hexahydro-2-pyridinecarboxylate;

(1S)-1-cyclohexyl-3-phenylpropyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)hexahydro-2-pyridinecarboxylate;

(22aS)-15,15-dimethylperhydropyrido[2,1-c][1,9,4]dioxazacyclononadecine-1,12,16,17-tetraone;

(24aS)-17,17-dimethylperhydropyrido[2,1-c][1,9,4]dioxazacyclohenicosine-1,14,18,19-tetraone;



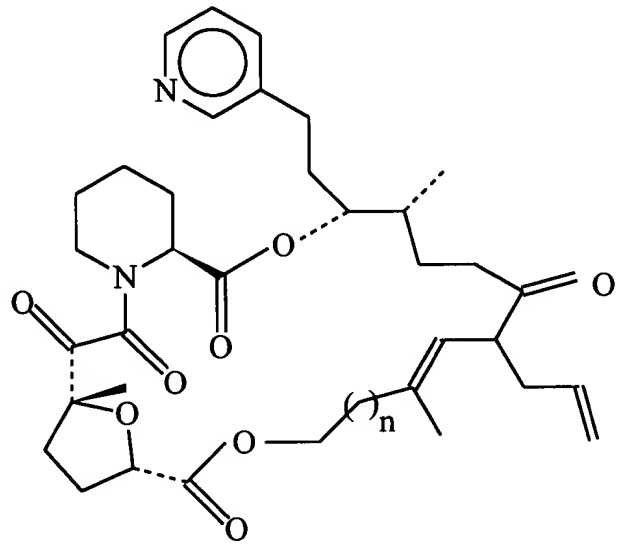
;

(3R,4R,23aS)-8-allyl-4,10-dimethyl-3-[2-(3-pyridyl)ethyl]-1,3,4,5,6,7,8,11,12,15,16,17,18,20,21,22,23,23a-octadecahydro-14H-

pyrido[2,1-c][1,10,4]dioxazacycloicosine-1,7,14,17,18-pentaone;

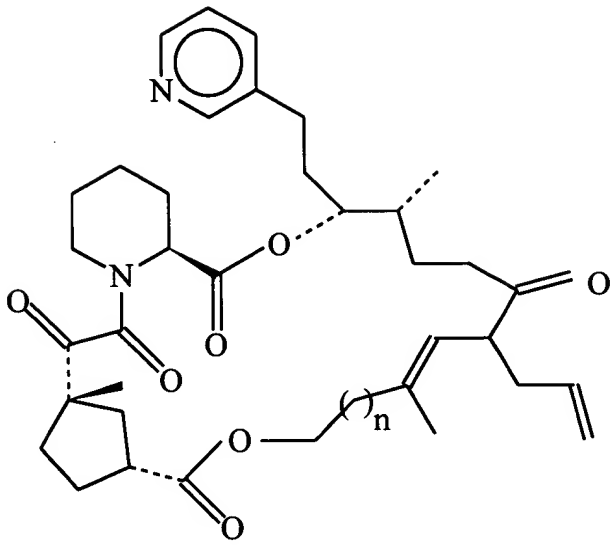
(3R,4R,24aS)-8-allyl-4,10-dimethyl-3-[2-(3-pyridyl)ethyl]-1,3,4,5,6,7,8,11,12,14,15,16,17,18,19,21,22,23, 24,24a-icosahydropyrido[2,1-c] [1,11,4]dioxazacyclohenicosine-1,7,14,18,19-pentaone;

(3R,4R,25aS)-8-allyl-4,10-dimethyl-3-[2-(3-pyridyl)ethyl]-1,3,4,5,6,7,8,11,12,15,16,17,18,19,20,22,23, 24,25,25a-icosahydro-14H-pyrido[2,1-c] [1,12,4]dioxazacyclodocosine-1,7,14,19,20-pentaone;



wherein n is 1; 2; or 3;

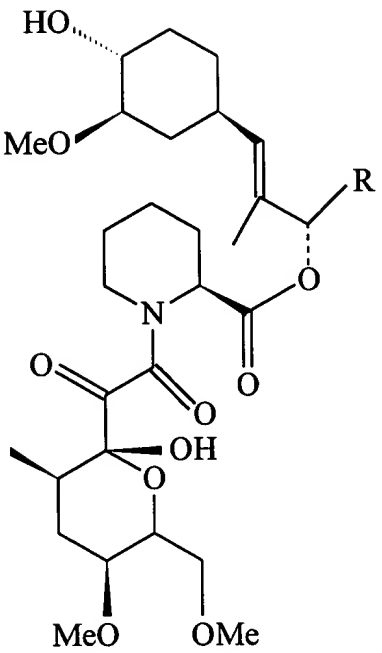
T, 1370
10 & cont



wherein n is 1; 2; or 3;

137 D

T.1380



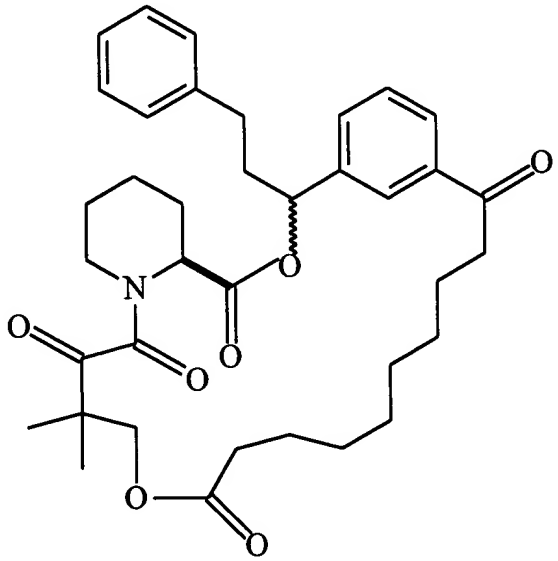
;

(1R)-1-(3-benzoylphenyl)-3-phenylpropyl (1R)-2-(3,3-dimethyl-2-oxopentanoyl)cyclohexane-1-carboxylate;

(1R)-1-[3-(diallylcarbamoyl)phenyl]-3-phenylpropyl;

(1R)-2-(3,3-dimethyl-2-oxopentanoyl)cyclohexane-1-carboxylate;

T.1381



;

ethyl 1-(2-oxo-3-phenylpropanoyl)-2-piperidinecarboxylate;

ethyl 1-pyruvoyl-2-piperidinecarboxylate;

ethyl 1-(2-oxobutanoyl)-2-piperidinecarboxylate;

ethyl 1-(3-methyl-2-oxobutanoyl)-2-piperidinecarboxylate;

ethyl 1-(4-methyl-2-oxopentanoyl)-2-piperidinecarboxylate;

ethyl 1-(3,3-dimethyl-2-oxobutanoyl)-2-piperidinecarboxylate;

ethyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate;

4-[2-(ethyloxycarbonyl)piperidino]-2,2-dimethyl-3,4-dioxobutyl acetate;

ethyl 1-[2-(2-hydroxytetrahydro-2H-2-pyranyl)-2-oxoacetyl]-2-piperidinecarboxylate;

10 cont

ethyl 1-[2-(2-methoxytetrahydro-2H-2-pyranyl)-2-oxoacetyl]-2-piperidinecarboxylate;

ethyl 1-[2-(1-hydroxycyclohexyl)-2-oxoacetyl]-2-piperidinecarboxylate;

ethyl 1-[2-(1-methoxycyclohexyl)-2-oxoacetyl]-2-piperidinecarboxylate;

ethyl 1-(2-cyclohexyl-2-oxoacetyl)-2-piperidinecarboxylate;

ethyl 1-(2-oxo-2-piperidinoacetyl)-2-piperidinecarboxylate;

ethyl 1-[2-(3,4-dihydro-2H-6-pyranyl)-2-oxoacetyl)-2-piperidinecarboxylate;

ethyl 1-(2-oxo-2-phenylacetyl)-2-piperidinecarboxylate;

ethyl 1-(4-methyl-2-oxo-1-thioxopentyl)-2-piperidinecarboxylate;

3-phenylpropyl 1-(2-hydroxy-3,3-dimethylpentanoyl)-2-piperidinecarboxylate;

(1R)-1-phenyl-3-(3,4,5-trimethoxyphenyl)propyl 1-(3,3-dimethylbutanoyl)-2-piperidinecarboxylate;

(1R)-1,3-diphenylpropyl 1-(benzylsulfonyl)-2-piperidinecarboxylate;

3-(3,4,5-trimethoxyphenyl)propyl 1-(benzylsulfonyl)-2-piperidinecarboxylate;

1-(2-[(2R,3R,6S)-6-[(2S,3E,5E,7E,9S,11R)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyltetrahydro-2H-2-pyranyl)-2-oxoacetyl)-2-piperidinecarboxylic acid;

methyl 1-(2-[(2R,3R,6S)-6-[(2S,3E,5E,7E,9S,11R)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyltetrahydro-2H-2-pyranyl)-2-oxoacetyl)-2-piperidinecarboxylate;

isopropyl 1-(2-[(2R,3R,6S)-6-[(2S,3E,5E,7E,9S,11R)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyltetrahydro-2H-2-pyranyl)-2-oxoacetyl)-2-piperidinecarboxylate;

benzyl 1-(2-[(2R,3R,6S)-6-[(2S,3E,5E,7E,9S,11R)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyltetrahydro-2H-2-pyranyl)-2-oxoacetyl)-2-piperidinecarboxylate;

1-phenylethyl 1-(2-[(2R,3R,6S)-6-[(2S,3E,5E,7E,9S,11R)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyltetrahydro-2H-2-pyranyl)-2-oxoacetyl)-2-

140 D

piperidinecarboxylate;

(Z)-3-phenyl-2-propenyl 1-(2-[(2R,3R,6S)-6-[(2S,3E,5E,7E,9S,11R)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyltetrahydro-2H-2-pyranyl)-2-oxoacetyl)-2-piperidinecarboxylate;

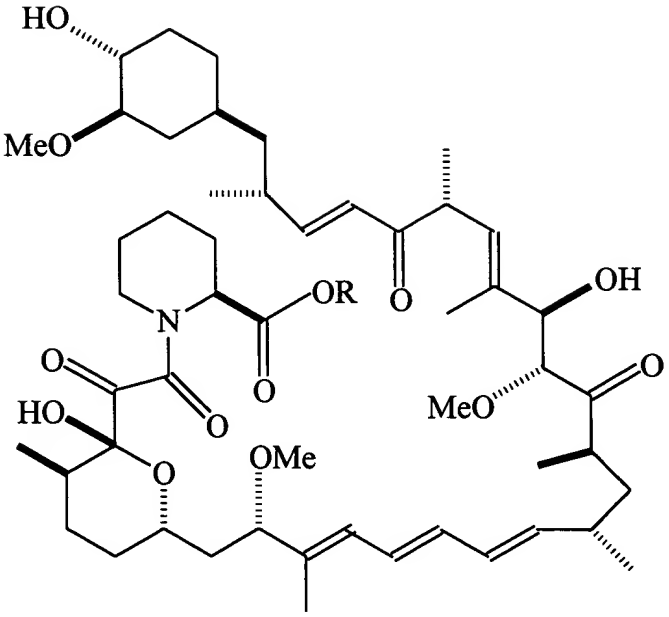
3-(3,4-dimethoxyphenyl)propyl 1-(2-[(2R,3R,6S)-6-[(2S,3E,5E,7E,9S,11R)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyltetrahydro-2H-2-pyranyl)-2-oxoacetyl)-2-piperidinecarboxylate;

N2-benzyl-1-(2-[(2R,3R,6S)-6-[(2S,3E,5E,7E,9S,11R)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyltetrahydro-2H-2-pyranyl)-2-oxoacetyl)-2-piperidinecarboxylate;

N2-(3-phenylpropyl)-1-(2-[(2R,3R,6S)-6-[(2S,3E,5E,7E,9S,11R)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyltetrahydro-2H-2-pyranyl)-2-oxoacetyl)-2-piperidinecarboxylate;

141 D

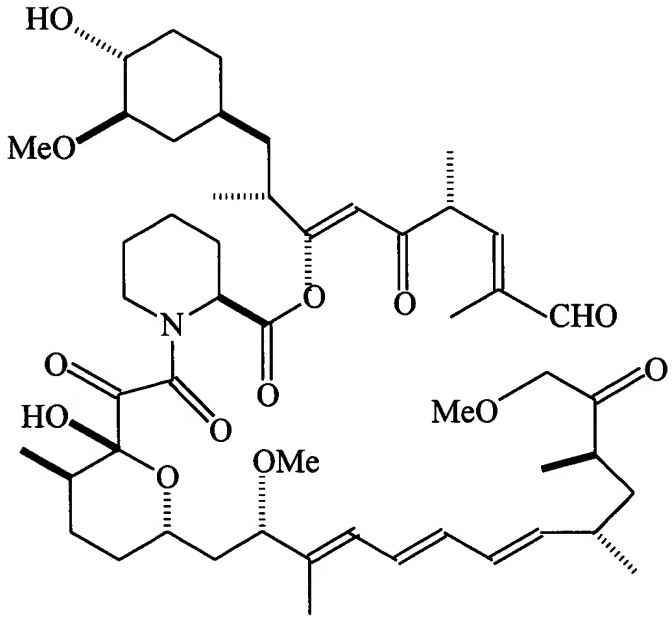
T,1420



108 cont

wherein R is methyl (Me); or benzyl (Bn);

T,1421



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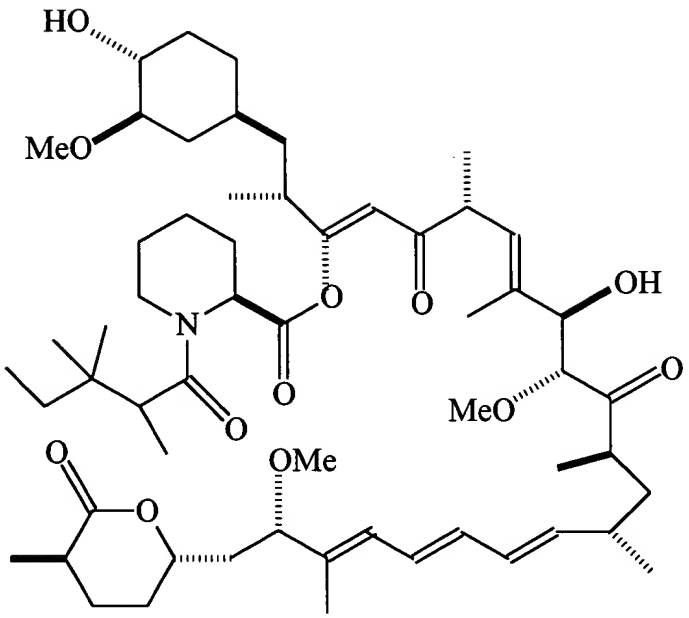
T1430



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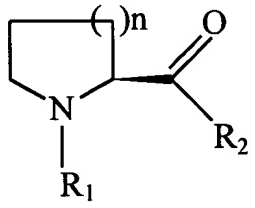
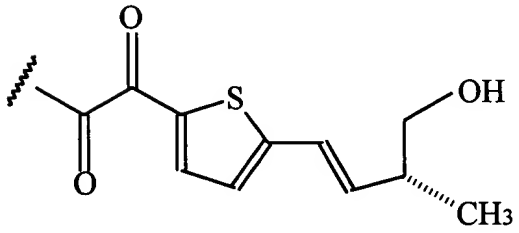
208 cont



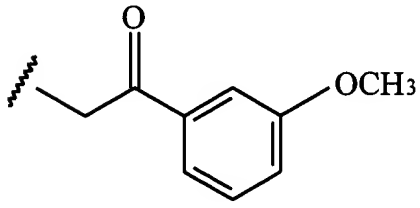
wherein n = 2,

R_1 =



T1431

or



143

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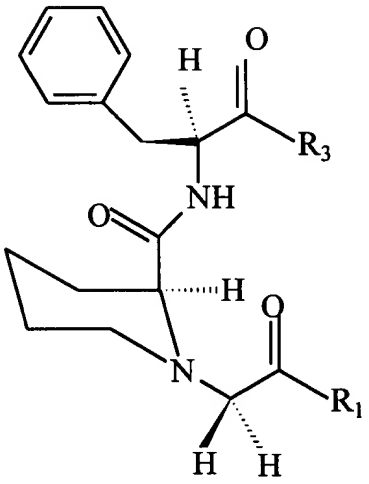
and

R_2 = Phe-o-tert-butyl;

T,1440



20 & cont.

wherein

R_1 = m-OCH_3Ph, R_3 = Val-o-tert-butyl;

R_1 = m-OCH_3Ph, R_3 = Leu-o-tert-butyl;

T,1441

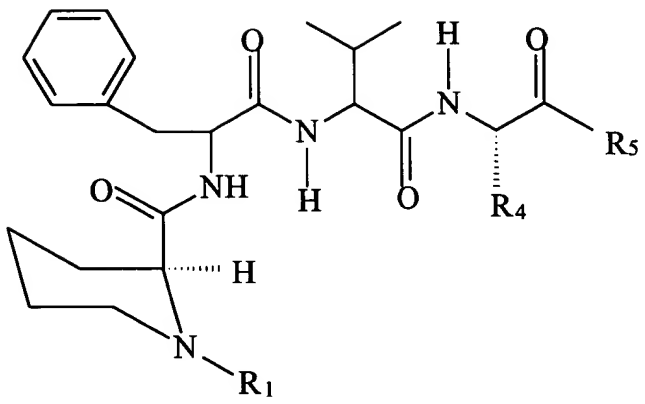
R_1 = m-OCH_3Ph, R_3 = Ileu-o-tert-butyl;

R_1 = m-OCH_3Ph, R_3 = hexahydro-Phe-o-tert-butyl;

R_1 = m-OCH_3Ph, R_3 = allylalanine-o-tert-butyl;

R_1 = B-naphthyl, R_3 = Val-o-tert-butyl;

T1145D



wherein R_1 = $CH_2(CO)$-m-OCH_3Ph

R_4 = CH_2Ph

R_5 = OCH_3;

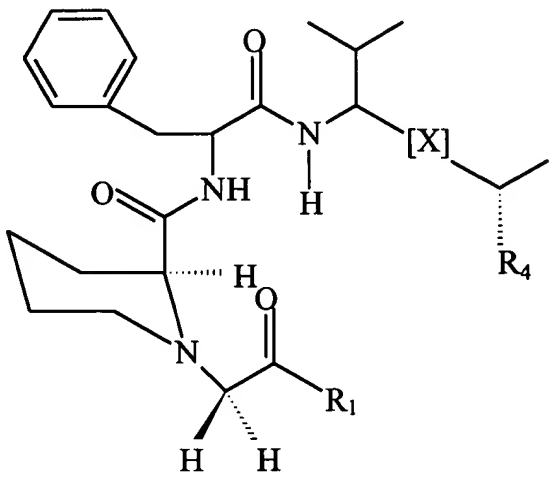
or

R_1 = $CH_2(CO)$-B-naphthyl

R_4 = CH_2Ph

R_5 = OCH_3;

T1145I



145 D

wherein

R_1 = m-OCH_3Ph

X = trans-CH=CH

R_4 = H

Y = OC(o)Ph;

R_1 = OCH_3Ph

X = trans-CH=CH

R_4 = H

Y = $OC(o)CF_3$;

108 cont

R_1 = m-OCH_3Ph

X = trans-CH=CHI

R_4 = -

Y = -;

R_1 = m-OCH_3Ph

X = trans-CH=CH

R_4 = H

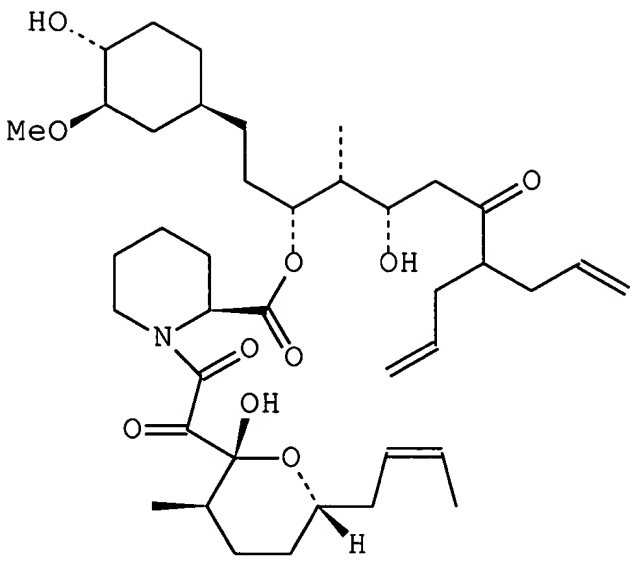
Y = $OCH_2CH=CH_2$;

R_1 = m-OCH_3Ph

X = C=O

R_4 = H

Y = Ph;



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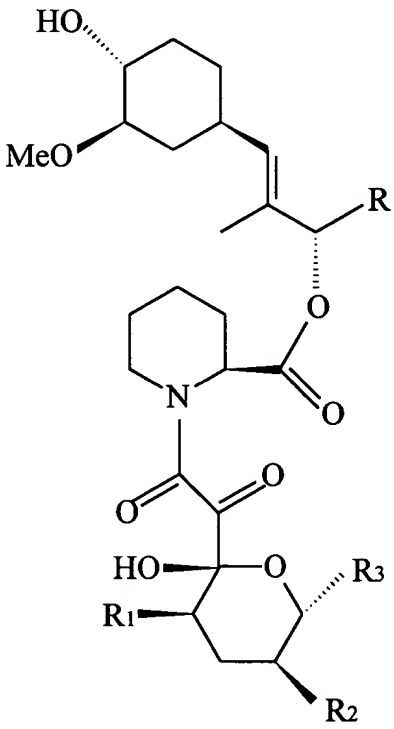

wherein

T.1480

R_1 = H, R_2 = OMe, and R_3 = CH_2OMe;

R_1 = H, R_2 = H, and R_3 = H;

R_1 = Me, R_2 = H, and R_3 = H;

(E)-3-(3,4-dichlorophenyl)-2-propenyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate;

(E)-3-(3,4,5-trimethoxyphenyl)-2-propenyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate;

(E)-3-phenyl-2-propenyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate;

10 cont

(E)-3-((3-(2,5-dimethoxy)-phenylpropyl)phenyl)-2-propenyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate;

4-(4-methoxyphenyl)butyl 1-(2-oxo-2-phenylacetyl)-2-piperidinecarboxylate;

3-phenylpropyl 1-(2-oxo-2-phenylacetyl)-2-piperidinecarboxylate;

3-(3-pyridyl)propyl 1-(2-oxo-2-phenylacetyl)-2-piperidinecarboxylate;

3-(3-pyridyl)propyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate;

4-phenyl-1-(3-phenylpropyl)butyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate;

4-(4-methoxyphenyl)butyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate;

1-(4-methoxyphenethyl)-4-phenylbutyl 1-(3,3-dimethyl-2-

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D

oxopentanoyl)-2-piperidinecarboxylate;

3-(2,5-dimethoxyphenyl)propyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate;

3-(1,3-benzodioxol-5-yl)propyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate;

1-phenethyl-3-phenylpropyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate;

4-(4-methoxyphenyl)butyl 1-(2-cyclohexyl-2-oxoacetyl)- 2-piperidinecarboxylate;

3-cyclohexylpropyl 1-(2-cyclohexyl-2-oxoacetyl)-2-piperidinecarboxylate;

3-phenylpropyl 1-(2-cyclohexyl-2-oxoacetyl)-2-piperidinecarboxylate;

3-cyclohexylpropyl 1-(3,3-dimethyl-2-oxobutanoyl)-2-piperidinecarboxylate;

3-phenylpropyl 1-(3,3-dimethyl-2-oxobutanoyl)-2-piperidinecarboxylate;

4-(4-methoxyphenyl)butyl 1-(3,3-dimethyl-2-oxobutanoyl)-2-piperidinecarboxylate;

4-phenyl-1-(3-phenylpropyl)butyl 1-(3,3-dimethyl-2-oxobutanoyl)-2-piperidinecarboxylate;

Way-124,666;

rapamycin;

Rap-Pa; and

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D

SLB-506,

or a pharmaceutically acceptable salt, ester, or solvate thereof,

wherein the nerve-related vision disorder is selected from the group consisting of visual impairments; orbital disorders; disorders of the lacrimal apparatus; disorders of the eyelids; disorders of the conjunctiva; disorders of the cornea; cataract; disorders of the uveal tract; disorders of the retina; disorders of the optic nerve or visual pathways; free radical induced eye disorders and diseases; immunologically-mediated eye disorders and diseases; eye injuries; and symptoms and complications of eye disease, eye disorder, and eye injury.

108 cont.

2 103. (Once amended) The method of claim 1 102, wherein the compound is Way-124,666.

3 104. (Once amended) The method of claim 1 102, wherein the compound is rapamycin.

4 105. (Once amended) The method of claim 1 102, wherein the compound is Rap-Pa.

5 106. (Once amended) The method of claim 1 102, wherein the compound is SLB-506.

150 D

Table E

Efficacy of representative compounds from different immunophilin ligand series in protecting retinal ganglion cell axons from degeneration following optic nerve transection

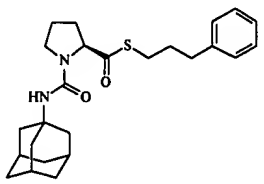
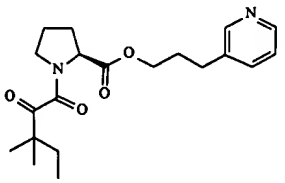
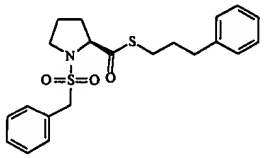
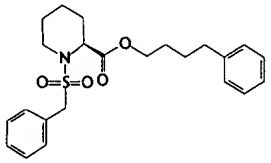
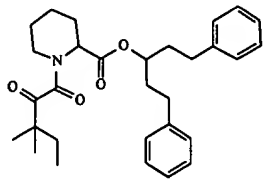
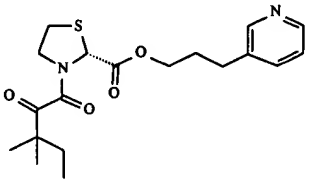
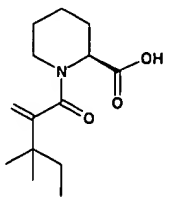
Compound	Structure	Comments	RT97+RGC axon density 14 days after ON transection (% ON axons rescued)
B		Adamantyl Thioester of urea K_i Rotamase=149 nM Clearance=? µl/min.	100.0% ±5.2% SEM
A GPI 1046		Ester Ki rotamase=7.5 nM Clearance=63.8 µl/min.	60.5% ±3.9 SEM
C		Sulfonamide Ki rotamase=107 nM Clearance=31.1 µl/min.	60.4% ±3.1% SEM
D		Pipecolic sulfonamide Ki rotamase= nM Clearance= µl/min.	58.4% ±6.4% SEM
E		Ester of pipecolic acid Ki rotamase=20 nM Clearance=41.8 µl/min.	56.6% ±9.4% SEM
F		Proline heterocycle Analog of GPI 1046 Ki rotamase=272 nM Clearance=? µl/min	55.1% ±5.9% SEM
G		Pipecolic acid dimethyl ketone Ki rotamase>10,000 nM Clearance=? µl/min.	34.0% ±4.8% SEM

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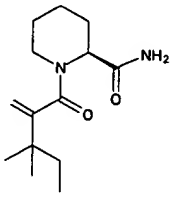
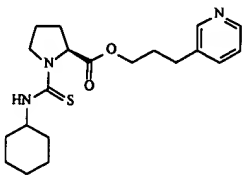
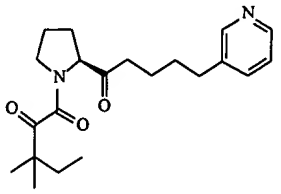
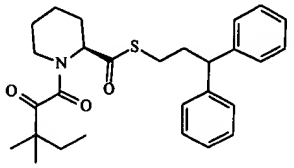
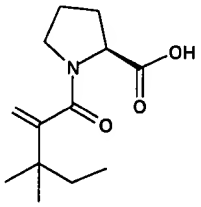
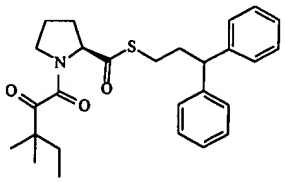
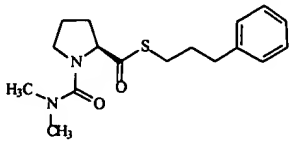
Table E continued

Compound	Structure	Comments	RT97+RGC axon density 14 days after ON transection (% ON axons rescued)
H		Ki rotamase= nM Clearance=? µl/min.	30.3% ±8.0% SEM
I		Ester of Thiourea Ki rotamase=131 nM Clearance=8.0 µl/min.	23.8% ±5.3 SEM
J		Ketone analog of GPI 1046 Ki rotamase=210 nM Clearance=1.5 µl/min.	15.8% ±4.8% SEM
K		Pipecolic acid Thioester Ki rotamase=86 nM Clearance=4.5 µl/min.	13.0% ±4.2% SEM
L		Prolyl acid Ki rotamase= >7743 nM Clearance=5.2 µl/min.	7.8% ±3.0% SEM
M		Thioester Ki rotamase=7 nM Clearance=12.5 µl/min.	-6.3% +3.9% SEM
N		Ki rotamase=722 nM Clearance=21.9 µl/min.	